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PROLIXIN AND PERMITIL

Fluphenazine, one of the newer phenothiazines, is available under the trade names Prolixin (Squibb) and Permitil (White). Prolixin is offered for the treatment of "mental disorders" in doses of 2.5 to 10 mg. daily, with the admonition that dosages above 20 mg. daily should be used with caution; the manufacturer lists many side effects such as are encountered with other phenothiazines, including dystonic and dyskinetic reactions, parkinsonism, akathisia, lethargy, and hypotension. Permitil, on the other hand, is offered "for control of emotional stress and anxiety," and the manufacturer recommends doses totaling not more than 2 mg. per day; at such dosage levels, it is claimed, "side effects have been observed infrequently or not at all."

PROLIXIN - The drug acts rapidly and it appears to be effective in many psychotic patients, though side effects are frequent. Whether or not it has any greater value in the treatment of psychoses than previously available phenothiazines is difficult to determine from published studies. In one study with placebo but not double-blind controls (L. D. Hankoff, et al., Dis. Nerv. System, 21:467, 1960), doses of 2 to 20 mg. of fluphenazine per day were more effective than a placebo in depressed and paranoid patients, but less effective than a placebo in patients with anxiety.

Other studies show remarkable improvement in a high percentage of patients, but in these studies controls were poor or lacking, standards for determining degree of improvement were vague, and details of methods and results given in the reports are grossly inadequate. One report states: "Of the 188 patients treated with fluphenazine 141 were considered to be improved, and of these 77 showed much improvement." The difficulty of judging the significance of such results can be seen from a previous paragraph of the report which says: "Other therapeutic aids such as psychotherapy, change of milieu and electroshock therapy, were used in most cases. Barbiturates were frequently given at bedtime to the patients who required aid in sleeping. In addition, those patients who were believed unable to benefit from a phenothiazine tranquilizer were excluded from the study." (I. J. Taylor, Dis. Nerv. System, 21:169, 1960).

PERMITIL - As for fluphenazine in the form of Permitil, it is clear that very low doses are recommended because of the high frequency of side effects with larger doses. The evidence fails to establish that with the low doses rec-

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ommended, anything more than placebo effects can be expected in most patients. One study distributed in reprint form by the manufacturer reports successful results in 74 per cent of patients, but the study was entirely uncontrolled, and the doses of Permitil used ranged from 2 to 20 mg. in psychotic patients and from 1 to 5 mg. in psychoneurotic patients (F. J. Ayd, Jr., Current Ther. Res., 1:41, 1959). No figures are given relating results to dosage. In addition to such side effects as weakness, nausea, dizziness and hypotension, akathisia occurred in 30 per cent of the patients and parkinsonism in 10 per cent.

Because of the high rate of remission in psychoneurotic patients, especially when they are under a doctor's care and receiving therapy of any kind, and because of the great difficulty of judging degree of improvement, physicians should not be expected to accept any but rigidly controlled studies as proof of successful treatment of neurotic or psychosomatic disorders. Not one of the published studies with Permitil made use of adequate controls.

POTENCY - There is no disagreement with the claim that fluphenazine is highly potent on a milligram-for-milligram basis; but potency in itself has no therapeutic significance unless the reduced dosage is accompanied by diminution of unwanted effects. With the phenothiazine tranquilizers, particularly those having a piperazine side chain, such as fluphenazine, trifluoperazine (Stelazine) and prochlorperazine (Compazine), increased potency is usually associated with an increase rather than a decrease in extrapyramidal effects.

In general, the phenothiazine tranquilizing drugs show an appreciable incidence of serious or disabling effects such as dyskinesias, extrapyramidal symptoms, hypotension and akathisia. Some phenothiazines have also produced jaundice, agranulocytosis, leukopenia or granulocytopenia. The physician is willing to risk even serious side effects in the treatment of psychotic patients. The risks are too great, however, to justify the routine use of such drugs in the long-term management of neurotic disorders, particularly in the absence of proof of their effectiveness. In psychotic patients, large enough doses of the drug doubtless have therapeutic effect in many cases. Present evidence does not, however, warrant the routine substitution of fluphenazine for such well-tried drugs as chlorpromazine (Thorazine).

(The use of phenothiazines as antiemetics will be reviewed in a future issue of The Medical Letter.)

ANTICOAGULANT DRUGS AND SURGERY

"Anticoagulant drugs are contraindicated...before surgery of any kind." This statement, which appeared in a Medical Letter appraisal of oral anticoagulant drugs (1:85, Nov. 13, 1959), has been the subject of a great deal of discussion in the intervening months, and the problem has been further reviewed by Medical Letter consultants.

The AMA Council on Drugs states that anticoagulant drugs "should not be given to patients about to undergo surgery..." (New and Non-Official Drugs,

1960, p. 507). "Prescribers' Notes" of the British Ministry of Health, on the other hand, does not consider surgery a contraindication to anticoagulant therapy. Dr. Irving Wright, former president of the American Heart Association, takes a middle position, indicating the need for special caution in the use of anticoagulants only in procedures leaving raw surfaces, procedures with tube drainage, and after operations on the brain and the spinal cord.

Only large-scale controlled studies can resolve these differences. Until such studies have been performed, the following recommendations seem justified:

(1) Prior to elective surgery, anticoagulants should be discontinued in most patients who have been on long-term anticoagulant therapy, and resumed 36 to 48 hours after the surgery. In the occasional patient in whom the risk of discontinuing anticoagulants appears to be excessive, oral drugs should be reduced and stopped, and intravenous heparin substituted.

(2) In emergency surgery in patients on oral anticoagulant drugs, about 50 mg. of vitamin K_1 (Mephyton - Merck; Konakion - Roche) is given intravenously to restore normal prothrombin activity and heparin is then substituted for the oral drugs. Therapy with heparin is usually more easily and accurately controlled than with oral anticoagulant drugs, and is probably safer. Protamine Sulfate NF or Polybrene (Abbott) should be available at all times to neutralize excessive anticlotting effects of heparin. Following recovery from surgery - at about the time sutures are removed - oral anticoagulant drugs can be restored.

Stopping or lowering the dose of oral anticoagulant drugs before surgery raises the question of possible "rebound" of the blood coagulation factors. Such rebound has often been postulated but never definitively proved.

ALBUSTIX

Albustix (Ames) provides a simple and reliable test for urine protein. The Albustix paper strip is dipped into the urine and the resulting color compared with a chart representing 0, 30, 100, 300 and 1000 or more mg. of protein per 100 cc. Color development is immediate. The strips are impregnated with tetrabromphenol blue and citrate buffered at approximately pH 3.

The Albustix strips compare satisfactorily in reliability with the older conventional methods. The test is unaffected by turbidity of the urine or by certain drug metabolites which may give false-positive readings in the conventional tests. Its sensitivity is in the same range as that of the sulfosalicylic acid test and the heat and acetic acid test. The strips react with hemoglobin and Bence-Jones protein as well as with albumin and globulin. False-positive readings are obtained only in strongly buffered urine of high alkalinity such as might be caused by ammonia-producing bacterial contaminants if the urine is not fresh.

Uristix (Albustix plus enzymatic test for glucose) and Combistix (Uristix plus pH indicator) have been used advantageously in routine urinalysis both in office practice and in hospitals. Albustix strips cost the physician about $2.40 for 120; Uristix strips, about $3.60 for 125; Combistix strips, about $4.80 for 125.

PROTAMIDE

A sterile colloidal solution of denatured proteolytic enzyme from hog gastric mucosa (Protamide - Sherman) is promoted for "relief and recovery from pain and other symptoms caused by posterior nerve-root disorders." Specifically, the manufacturer recommends its use in neuritis of varying etiology, including herpes zoster, and for the lightning pains of tabes dorsalis. In view of the inadequacy of the controls in studies which found this drug to be effective in neuritides of highly variable, unpredictable, and usually self-limited course, and in view of the absence of a scientific rationale for its use, The Medical Letter can only conclude that Protamide is of no value in these disorders.

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